REJOINDER: COHEN'S RESPONSE TO "ON THE DISCREPANCY BETWEEN EPIDEMIOLOGIC STUDIES IN INDIVIDUALS OF LUNG CANCER AND RESIDENTIAL RADON AND COHEN'S ECOLOGIC REGRESSION"

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REJOINDER

Cohen's ecologic regression has prompted a continuing exchange since it was first published nearly a decade ago. Throughout this period, Cohen has consistently failed to appreciate the widely recognized point, illustrated by Lubin (1998), as well as by Greenland and Robins (1994), Muirhead et al. (1991), Piantadosi et al. (1988), Stidley and Samet (1993, 1994) and others, that ecologic studies are inherently flawed and cannot be used to evaluate an exposure-response relationship for individuals. Cohen's insistence that his negative ecologic regression of county lung cancer mortality rates on county mean radon levels is incompatible with a linear no-threshold relationship for radon and lung cancer for individuals is just wrong, because it does not account for limitations in the ecologic approach, namely, the county-level relationship may be biased for the true relationship.

In addition to the many issues raised by other authors, three points can be made. First, when dealing with county-level data on radon and lung cancer rates, the ecologic fallacy always applies. Cohen's repeatedly asserting that the ecologic fallacy does not apply does not make it so. The ecologic fallacy refers to the erroneous belief that a linear no-threshold model for lung cancer risk from radon for individuals implies that counties with higher mean radon levels (even with Cohen's *ad hoc* adjustment based on a fixed 12-fold smoking effect) have higher lung cancer rates or, alternatively, that the county-level exposure-response relationship necessarily reflects the true relationship for individuals. In fact, the association for radon exposure and lung cancer risk at the individual level can easily be distorted by the correlation between radon and other lung cancer risk factors within counties to produce a negative trend in county rates. This result is often called cross-level bias.

Second, cross-level bias cannot be "eliminated" with the addition of county-level covariates to an ecologic regression. Moreover, my paper shows that correlations within county (radon and smoking or any other lung cancer risk factors) can dramatically bias the county-level relationship. Thus, no valid inference about the true association for individuals can be assured from an ecologic regression. In particular, Cohen's analysis showing that counties with higher lung cancer mortality have lower mean radon levels has no etiologic significance or public health relevance, since that association easily could be due to cross-level bias.

It is, of course, not *necessarily* true that, in Cohen's data, a true increase in risk with increasing radon exposure for individuals has been distorted by cross-level bias into a decreasing trend at the county level, but it easily *could* be true, which means that Cohen's data by themselves have little or no evidential value. Alternatively, a positive trend at the county level, by itself, also would provide limited information.

Third, suppose that Cohen's results were indeed free of cross-level bias. Then his regression predicts a protective effect for lung cancer from constant exposure below 200–250 Bq m^{-3} (see figure 1, Cohen 1998). This prediction is contradicted by all relevant analytic studies. Fig. 1 shows relative risks (RRs) from eight indoor radon studies, the RR trend from pooled data from all cohort studies of radon-exposed underground miners with exposures limited to less than 50 Working Level Months, and the RR trend from Cohen's ecologic regression (see Lubin and Boice 1997 for details). The analytic studies, which measured radon and/or radon progeny levels and directly estimated exposure to individuals, show either no association or positive associations. Furthermore, among the eight indoor studies and the 11 cohort studies of miners not a single study has produced even the suggestion of a large negative exposure-response relationship on the order found in the ecologic analysis by Cohen.

The flaw in ecologic regression is intrinsic in the methodology, not in the process, which is the reason that ecologic studies are used only for generating hypotheses. While no observational study (ecologic, case-control or cohort study) is perfect, the ecologic design has the least

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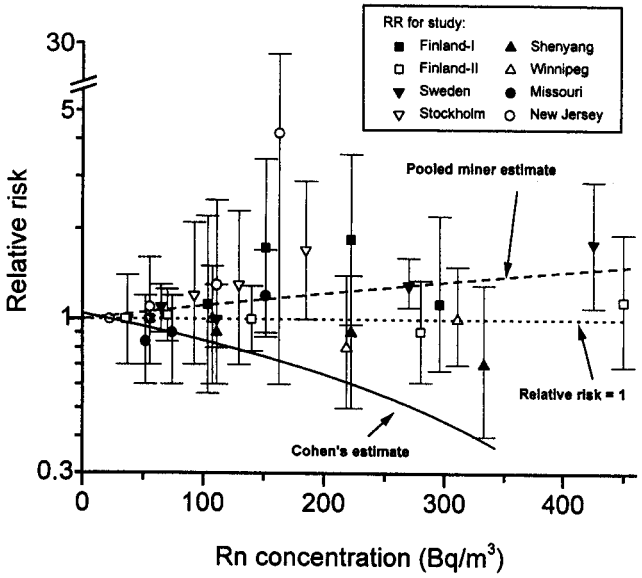

Fig. 1. Relative risks (RRs) from eight indoor radon studies, the RR trend from studies of miners with exposures restricted to <50 Working Level Months, and the RR trend from Cohen's ecologic regression (adjusted to pass through 22.2 Bq m^{-3}, the mean of the lowest RR category in the indoor studies) (Lubin and Boice 1997).

a priori claim to validity. It may never be possible to state categorically what factor or factors caused Cohen's negative trend. Nevertheless, because of the well-recognized limitations of the ecologic approach, Cohen's results are not believable when compared with the 19 analytic case-control and cohort studies and should not be allowed to negate the growing body of evidence suggesting a small increase in lung cancer risk from indoor radon.

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